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EXAMINER

SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/910,432

Applicant(s)

WAUGH ET AL.

Examiner

Richard Schnizer, Ph. D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 September 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 and 22-39 is/are pending in the application.
- 4a) Of the above claim(s) 5-9, 13-18, 22 and 28-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 10-12, 19, 20, 23-27 and 39 is/are rejected.
- 7) ☐ Claim(s) 2-4 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

An amendment was received and entered on 9/7/06.

Claim 21 was cancelled. Claims 1-20 and 22-39 remain pending.

In the response filed 8/8/05, Applicant elected group 1 and the species of a composition comprising a non-covalent association complex of a positively charged backbone polymer having positively charged branching groups of the formula (gly)_p-RGRDDRRQRRR-(gly)_q (SEQ ID NO:19), a negatively charged backbone comprising a plurality of attached targeting moieties, and a negatively-charged backbone having a plurality of attached BOTOX molecules. Claims 1-4, 10, 11, 12, 15-17, and 39 read on this species, and the species was found to be free of the art.

After further search it was determined that embodiments of the invention comprising a plurality of therapeutic or cosmeceutical agents listed in the specification, including BOTOX (botulinum toxin) molecules, attached to a negatively charged backbone and complexed with a positively charged backbone and a second negatively charged backbone (claims 2-4) are free of the art of record. Accordingly, the Office has selected another species for consideration, i.e. a composition comprising a non-covalent association complex of a positively charged backbone that is a peptide comprising a positively charged branching group that is a fragment of HIV-TAT, at least one member selected from the group consisting of RNA, DNA, ribozymes, modified oligonucleotides and cDNA encoding a selected transgene, and DNA encoding at least one persistence factor, wherein the fragment of HIV-TAT is other than:

1. $G_{n1}R_{n2}$ with $n1$ = an integer from about 0 to about 20, and $n2$ = an odd integer from about 5-25,
2. G_p -RGRDDRRQRRR- G_q , (SEQ ID NO:19), and
3. G_p -YGRKKRRQRRR- G_q , (SEQ ID NO:20), as set forth in the restriction requirement of 5/19/04.

Claims 1, 10-12, 19-21, 23-27, and 39 read on this species.

In the previous Action the Office erroneously indicated that claims 15-17 read on this species. Claims 15-17 are drawn to HIV-TAT fragments 2 or 3 above, and so do not read on the species under consideration. Accordingly claims 15-17 are withdrawn.

Claims 1, 2-4, 10-12, 19, 20, 23-27 and 39, are under consideration in this Office Action.

In the response filed 9/7/06, Applicant listed the status of claims 2-4 as "withdrawn". Actually, claims 2-4 are under consideration, and are objected to as depending from a rejected claim but would be allowable if rewritten in independent form incorporating all the limitations of claim 1.

Rejections Withdrawn

The rejection of claim 12 for incorporation of new matter is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite because it is unclear what is intended by the term "length". The specification does not define this term and it is not clear what standard should be used to determine length. One standard that could be used is the length of the backbone in angstroms, another is the length of the backbone in terms of the number of monomers comprised, still another is the length of the backbone after it has folded as a result of interactions with the other members of the complex. It is also unclear if, in the situation where a complex comprises more than one of a given negatively charged backbone, all of the copies of that backbone should be used in the calculation. Because one of skill does not know which standard to apply, or what are the limits of how the length calculations can be performed, one cannot know the intended metes and bounds of the claims.

Response to Arguments

Applicant's arguments filed 9/7/06 have been fully considered but they are not persuasive.

Applicant addresses the rejection at pages 13 and 14 of the response. Applicant notes that the specification provides a way to measure length at page 7, lines 9-11, i.e. length ratios can be determined based on molecular studies of the components or can

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be determined from the masses of the components. This is unpersuasive. It appears that Applicant is arguing that length can be determined using any molecular study, or alternatively, by molecular weight. However, it is clear that that "molecular studies" of a given molecule may give a different length than one would arrive at based on molecular weight. For example, a molecular study may provide a length of in terms of particle diameter or Stokes radius that is not directly related to the linear length, or the mass, of a molecule, but is more a function of molecular folding. It is unclear which of these means, linear length, mass, or molecular study, one should use in determining the limits of the claim. However, it is clear that the same molecule may have different length measurements depending on how one takes the measurement. Therefore one of skill in the art cannot know the metes and bounds of the claim.

Applicant also asserts that only a single copy of a particular group (b) member should be used to calculate the length of the positively charged backbone required in claim 10, because one wishing to practice the invention would select a specific group (b) member with a defined length in terms of repeating subunits, and could do so before the positively charged backbone is mixed with the group (b) members. Applicant concludes that the actual amount of positively charged backbone relative to the actual amount of group (b) members in a given mixture is not relevant to determining whether the length limitation of claim 10 is satisfied. This unpersuasive because Applicant has presented no reason why one of skill in the art would choose to interpret the claim in this way instead of any other way. Even if one decided to use mass in Daltons of all of the components to determine length, it remains unclear whether the claim requires a

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ratio of lengths in a given complex, or a ratio of length of all the components selected prior to complex formation. In other words, there are two different interpretations of the claims:

1) the claim requires that, in a given complex of a positive backbone and negatively charged backbone species, the positively charged backbone must be 1-4 times as long as the combined lengths of all of all the negatively charged backbone species to which it is bound, or alternatively as Applicant argues

2) the claim requires that one selects a positively charged backbone and group (b) members such that the positively charged backbone is 1-4 times as long as the combined lengths of the group (b) members, regardless of how many, and what type, of members actually bind to a backbone to form a complex.

Applicant has provided no coherent reason why one of skill in the art would reject one definition in favor of the other, or why the meaning of the claim would be clear to one of skill in the art. There is no basis in the claim for limiting the calculation by using only one member of each particular set of negatively charged backbones. On what basis can Applicant exclude the embodiment wherein the positively charged backbone is long enough and is present in sufficient molar excess, relative to the negative backbones, to bind all of the negative backbones in solution, including a plurality of each type, and still satisfy the length limitation? The presentation of one interpretation of an ambiguous claim, without any reason to reject other alternative interpretations, does not constitute a persuasive argument. Finally, as discussed above, it is unclear

how one is intended to determine length in the first place, so determining ratios of lengths is problematic. For these reasons, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following rejection of claims 19 and 20 is applied to a generic form of the claims that is not limited to the species under consideration. This rejection demonstrates the unpatentability of the generic claims not limited to a species.

Claims 19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Illum (US Patent 5,744,166), as evidenced by GenBank Accession No. AAC54646.

Illum taught non-covalent complexes of polycations and nucleic acids. One exemplary polycation is polylysine modified with polyethylene glycol (PEG). See abstract; column 3, lines 16-19 and 57; and column 4, lines 4-7. The polylysine of Illum is considered to contain an efficiency group inasmuch as it contains fragments of HIV TAT. For example any lysine in the polylysine could be considered to correspond to a lysine in HIV-TAT. Note that GenBank Accession No. AAC54646 discloses that HIV TAT comprises three lysines at positions 68-70. These could be considered to correspond to any three lysines in the polylysine of Illum. Because any lysine in

polylysine would reasonably be expected to neutralize the negative charge of the nucleic acid of Illum, it would be expected to improve transfection efficiency, and could therefore be considered to be an efficiency group.

Thus Illum anticipates the claims.

The following rejections address the species under consideration.

Claims 1, 11, 12, 19, 20, 23, and 24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al (J. Biol. Chem. 262(10): 4429-4432, 1987) as evidenced by GenBank Accession No. M77788 (2005).

Wu taught non-covalent complexes of plasmid pSV2 CAT and polylysine, wherein the polylysine comprised an attached asialoorosomucoid targeting ligand. See abstract. The targeting ligand is considered to be an "efficiency group", as per claim 19. Plasmid pSV2 CAT comprises a selectable marker (beta lactamase, i.e. ampicillin resistance) as evidenced by GenBank Accession No. M77788. The selectable marker is considered to be a persistence factor as required by claim 1. Regarding claims 11, 12 and 21, polylysine is a polymer comprising attached positively charged branching groups, i.e. domains, which are also present in HIV-TAT because lysine side chains are present in HIV TAT.

This complex meets the limitations of species iii/iv because pSV2-CAT comprises the DNA required by group member 'iii', and the DNA encoding the persistence factor required by group member 'iv'. The plasmid of Wu is double stranded, so group member 'iv' is considered to be the strand of DNA that encodes the selectable marker

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beta lactamase, and group member 'iii' is considered to be the complementary DNA strand. Also note that the polylysine of Wu also comprises positively charged branching groups that are fragments of HIV-TAT, i.e. the positively charged lysine side chains. Further, any lysine side chain in the polylysine of Wu would reasonably be expected to neutralize the negative charge of the plasmid, so it would be expected to improve transfection efficiency, and could therefore be considered to be an efficiency group.

Thus Wu anticipates the claims.

Claims 1, 11, 12, 19, 20, 23, 24, and 27 stand rejected under 35 U.S.C. 102(b) as being anticipated by Cristiano et al (Proc. Nat. Acad. Sci. USA 90: 11548-11552).

Cristiano taught non-covalent complexes of polylysine and plasmid pCMV betaGal. The polylysine comprised attached targeting ligands, e.g. adenovirus and asialoorosomucoid. See abstract. The plasmid comprised a beta galactosidase reporter gene under control of a CMV promoter. See page 11548, column 2, second full paragraph. Plasmid pCMV beta gal comprises a selectable marker considered to be a persistence factor as required by claim 1. Regarding claims 11, 12 and 21, polylysine is a polymer comprising attached positively charged branching groups, i.e. domains, which are also present in HIV-TAT because lysine is present in HIV TAT. As in the preceding rejections, the targeting ligand is considered to be an attached efficiency group.

Thus Cristiano anticipates the claims.

Claims 1, 11, 12, 19, 20, 23-25, and 27 stand rejected under 35 U.S.C. 102(a) as being anticipated by Puls et al (Gene Therapy 6: 1774-1778, 1999), as evidenced by http://www.genlantis.com/catalog/product_line.cfm?product_family_key=13&product_line_key=54, retrieved from the internet on 9/2/05.

Puls taught non-covalent complexes of polylysine and plasmid pGeneGrip encoding green fluorescent protein (GFP) under the control of a CMV promoter and a selectable marker (see map on second page of attached product information downloaded from the web site cited above). The polylysine comprised an attached antibody targeting ligand. See abstract. Regarding claims 11, 12 and 21, polylysine is a polymer comprising attached positively charged branching groups, i.e. domains, which are also present in HIV-TAT because lysine side chains are present in HIV TAT.

Thus Puls anticipates the claims.

Response to Arguments

Applicant's arguments filed 9/7/06 have been fully considered as they might apply to the grounds of rejection set forth above, but they are not persuasive.

Applicant addresses the rejection over Illum at pages 14 and 15 of the response, and argues that Illum does not teach an "efficiency group". Applicant asserts that an in view of the specification, particularly page 9, lines 7-10 and Example 3, one of skill in the art would understand that "efficiency group" refers to the efficiency of cell membrane penetration ability. This is unpersuasive. Page 9, lines 7-10 indicate that the term "efficiency group" is used to refer to positively charged branching groups comprising -

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(gly)_{n1}-(arg)_{n2}, or HIV-TAT or fragments thereof, in which the subscript n1 is an integer of from 0 to 20. This passage does not limit use of the term “efficiency group” to these branching groups or convey in any way that the term is to be applied only to the genus of compounds that enhance membrane penetration. Example 3 describes the process of attaching (gly)_{n1}-(arg)_{n2} groups to polylysine, and the use of the resultant polymer in transfection. Applicant has not pointed to anything specifically in this section that would convey to one of skill in the art that the term “efficiency group” was to be understood as the group of compounds that increase the efficiency of cell membrane penetration, specifically, as opposed to those that enhance transfection generally. In any case, as discussed above in the rejection, Illum taught the use of polylysine, and HIV TAT comprises a tri-lysine fragment. As a result, polylysine is considered to comprise a fragment of HIV TAT. That fragment is considered to be an efficiency group because it helps to neutralize the negative charge of the nucleic acid to which it binds, thereby enhancing the likelihood that it will penetrate the cell membrane. For these reasons Applicant’s argument is unpersuasive and the rejection is considered to be proper.

Applicant addresses the rejection over Wu at pages 15-17 of the response. Applicant argues that it is improper and unwarranted to read the term “DNA” to include single strands of DNA of a plasmid as separate negatively charged backbones. Applicant asserts that one of skill in the art would understand the term DNA as recited in claim 1 to refer to hybridized double stranded DNA, not single stranded DNA, “because single stranded DNA does not exist stably in nature.” Applicant has also requested that the Examiner take official notice that the term “DNA” without further specification is

known by one of ordinary skill in the art to embrace both single and double stranded DNA, and to provide a corresponding reference in support.

Applicant's arguments are unpersuasive for several reasons. First, Applicant is arguing limitations that are not in the claims. The claims recite DNA, with no limitation regarding strandedness or separateness. "DNA" is an acronym for deoxyribonucleic acid. As is apparent from Applicant's arguments, deoxyribonucleic acid can occur in single and double stranded forms. Absent some limiting definition in the specification, the term "DNA" should be given its broadest reasonable interpretation. Because the term "DNA" itself has no implication at all regarding the number of strands present, it clearly embraces single stranded forms. Evidence of this comes from Applicant's own arguments, which recite the terms "single stranded DNA" and "double stranded DNA". Obviously, Applicant recognizes that these are both forms of DNA. On the other hand, Applicant has not pointed to any place in the specification that would lead one of skill in the art to believe that single strands of DNA were to be excluded from the claimed invention, and has provided no evidence whatsoever that one of skill in the art would understand the term "DNA" to exclude single stranded forms of DNA.

Second, it is unclear what is the relevance of whether or not single stranded DNA exists stably in nature. What does Applicant mean by "stably"? Why would it matter if single stranded DNA was inherently unstable? The cited art teaches plasmid DNA which is comprised of two non-identical negatively charged backbones, so the limitation requiring two non-identical negatively charged backbones is met. The claims have no requirement regarding stability.

Third, the statement that "single stranded DNA does not exist stably in nature" is factually incorrect. Single stranded DNA exists stably in nature in the form of single stranded DNA viruses such as parvoviruses, e.g. adeno-associated virus.

In view of the fact that the specification as filed provides no definition of the term "DNA" that would exclude "single stranded DNA" from types of DNA embraced by the term, and the fact that Applicant clearly understands that single stranded DNA is a form of DNA, it is unnecessary for the Examiner to take official notice, or to provide references, to support the position that the term "DNA" embraces both single and double stranded forms of deoxyribonucleic acid. On the contrary, the burden lies with Applicant to provide evidence that one of skill in the art would arbitrarily exclude single stranded DNA from the molecules embraced by the broad term "DNA". Nonetheless, solely in response to the request for a reference, Applicant's attention is directed to any one of US Patents 5190873, 5484720, 6297056, 6492152, 6667295, 6855513, or 6855802. As a courtesy, the relevant passages are set forth below.

US 5190873 states: "As used herein, the term "DNA sequences" encompasses both double-stranded DNA and single-stranded DNA containing information equivalent to that of the amino acid sequences as determined by the genetic code; such single-stranded sequences can be either in the sense strand orientation or the antisense strand orientation." See column 14, lines 28-34.

US 5484720 states: "As used herein, the term "desired DNA" is defined as any polydeoxynucleotide, including, e.g., double stranded DNA, single stranded DNA,

double stranded DNA wherein one or both strands is (are) composed of two or more fragments", etc. See column 4, lines 16-19.

US 6297056 states: "The DNA constructs of the invention also encompass all forms of nucleotide constructs including, but not limited to, single-stranded forms, double-stranded forms, hairpins, stem-and-loop structures and the like." See column 9, lines 14-18.

US 6492152 states "the term "DNA" includes cDNA, genomic DNA and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single-stranded, may be the coding strand or non-coding (anti-sense) strand." See column 2, lines 65-67.

US 6667295 states: "As used herein, the terms "DNA", "RNA", "gene," "polynucleotide molecule," "nucleotide sequence," "coding sequence," and "coding region" are intended to include both DNA and RNA polynucleotide molecules, and to refer to both single-stranded and double-stranded polynucleotide molecules." See column 8, lines 42-48.

US 6855513 states "The term "DNA" refers to deoxyribonucleic acid whether single- or double-stranded." See column 22, lines 44-45.

US 6855802 states: "The term "DNA fragments" is intended to mean single-stranded or double-stranded DNA, cDNA and/or RNA fragments." See sentence bridging columns 4 and 5.

Applicant also asserts at page 17 that the asialoglycoprotein targeting ligand of Wu is not an "efficiency group", reiterating their arguments used against the Illum

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reference. These arguments are unpersuasive for the reasons set forth above.

Applicant also argues that the targeting ligand of Wu merely improves binding specificity, not overall penetration through the membrane. This is unpersuasive. Fig. 3 of Wu provides objective evidence that the presence of the targeting ligand on polylysine increased uptake and expression of plasmid DNA over that seen with non-targeted polylysine. Compare lanes 2 and 4. Applicant argues that "this Figure does not illustrate increased cell penetration, only improved specificity towards target genes using ASOR-polylysine conjugate. Applicant does not see where Wu shows an increased cell membrane penetration by conjugating ASOR to polylysine." Applicants attention is directed to Fig. 3, lanes 2 and 4, which allow comparison of chloramphenicol acetyltransferase (CAT) activity in Hep G2 cells transfected with AsOR-polylysine-DNA complexes (lane 2) and polylysine DNA complexes (lane 4). In both lanes the DNA encodes CAT. Lane 2 shows abundant CAT activity, whereas lane 4 shows no detectable CAT activity. The clear result is that transfection with polylysine/DNA complexes occurred only in the presence of AsOR, and not in its absence. Therefore AsOR improved transfection efficiency. Because transfection requires penetration of the cell membrane AsOR, must have improved penetration of the cell membrane. With regard to claim 19 and dependents, requiring an efficiency group, the recited efficiency group can be considered to be the lysine side chains or the targeting ligand, because both of these can be considered to improve transfection efficiency, as discussed above.

Applicant addresses the rejection over Cristiano at pages 18 and 19 of the response. Applicant reiterates arguments regarding whether or not the term DNA

embraces single stranded DNA. These are unpersuasive for the reasons set forth above. Furthermore, Applicant has failed to address the fact that the adenovirus of Cristiano also comprises a DNA that is separate and distinct from the plasmid DNA.. This adenoviral DNA fulfills the limitation of group iii. Also, absent evidence to the contrary, the adenovirus of Cristiano encodes adenoviral preterminal protein, which is the only example of a persistence factor given in the instant specification, so it could also meet the limitation of group iv. So Cristiano taught embodiments in which the plasmid DNA corresponds to group member iii or iv, and the adenoviral DNA corresponds to group member iv or ii, respectively, but Applicant has not addressed this teaching in the response.

With regard to claims 19 and dependents, Applicant also does not see where Cristiano teaches an efficiency group as recited in claim 19. Applicant argues that amino acid side chains are structurally distinct from the conjugated branching groups described on page 9 of the specification. This is unpersuasive. The claims recite that the efficiency group can be any HIV -TAT fragment. As discussed above, HIV-TAT comprises a trilycine group, so any lysine pair or triplet in polylysine is a fragment of HIV-TAT, and meets the structural requirement of the claim. Applicant's argument that the office has not established that tandem lysines can function as an efficiency group is unpersuasive because the function must be considered to be inherent in the structure. If the claimed structure is taught, then the burden lies with Applicant to show that the claimed function is not inherent in the structure. In any case, as discussed above, one of skill in the art would see that lysine residues help to neutralize the negative charge of

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the nucleic acids to which they bind, thereby enhancing the likelihood that the nucleic acids will penetrate the cell membrane.

Applicant addresses the Puls reference at page 20 of the response. Applicant reiterates arguments that double stranded DNA does not comprise two negatively charged "members" as claimed, because one of ordinary skill in the art would consider the term DNA to refer to double stranded, hybridized DNA, and not to single stranded DNA. This is unpersuasive for the reasons set forth above and because double stranded DNA, by definition, has two strands, each of which is a negatively charged backbone. Applicant argues that the targeting ligand is not an efficiency group as recited in amended claim 19. This is true, however, the polylysine of Puls does contain an efficiency group as claimed in amended claim 19, i.e. the side chains of polylysine, or any lysine doublet or triplet in the polylysine. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 10-12, 19-21, 23, 24, 27 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (US Patent 5,744,166) in view of the 1998 Promega Catalog.

Illum taught non-covalent complexes of polycations and nucleic acids encoding genes. One exemplary polycation is DEAE-dextran of molecular weight 5000 to 40 X10⁶ Da, another is polylysine. See abstract; column 3, lines 16-32, and 57.

Illum did not require that the DNA must encode a persistence factor, or specify any relationship between the length of the polycation and the length of the nucleic acid.

One of ordinary skill in the art appreciates that in order to obtain expression of a gene, the gene must be operably linked to expression control sequences such as a promoter. This is conveniently achieved by inserting a gene of interest into a plasmid expression vector, such as the mammalian expression vectors disclosed at pages 262-265 of the 1998 Promega catalog. These plasmids have the added advantage of selectable markers that allow amplification of the plasmid in bacterial cells or selection of transfectants in mammalian cells. For the purpose of this rejection, selectable markers are considered to be persistence factors, as recited in claim 1. Furthermore, the SV40 poly A sites in each of the disclosed vectors are considered to be persistence factors inasmuch as they play a role in stabilizing expressed mRNAs, and the plasmid replication origins are also considered to encode persistence factors inasmuch as they allow replication of the plasmids. Note also that three of the four vectors include CMV promoter/enhancers. All of the plasmids are double stranded and so contain non-identical, negatively charged backbones.

It would have been obvious to one of ordinary skill in the art at the time of the invention to insert a gene of Illum into any one of the expression vectors disclosed by Promega, prior to incorporation into the composition of Illum. One would have been

motivated to do so because such plasmids facilitate handling of nucleic acids by allowing amplification in bacterial hosts prior to delivery to mammalian hosts.

Illum taught a range of DEAE-dextran of molecular weights from 5000 to 40×10^6 Da. Assuming a monomer molecular weight of about 217 Da per monomer, this corresponds to DEAE-dextran lengths of about 23 to about 184000 monomers. The "preferred " molecular weight of 500,000 Da corresponds to about 2300 monomers. The monomer lengths of the Promega plasmids carrying an average gene of 2 kb would range from about 5.6 to about 7.8 kb. It would have been obvious to one of ordinary skill in the art, as a matter of routine optimization to select the length of DEAE dextran that gave the optimal transfection efficiency for a given plasmid DNA. Absent evidence of unexpected results it would have been obvious to arrive at a length of DEAE-dextran, in monomers, in the range of about 1 to about 4 times the length the plasmid DNA in base pairs.

With regard to claim 11, note that DEAE-dextran is a polymer comprising attached positively charged branching groups.

With regard to claims 11, 19, and dependents, note that Illum also exemplified polylysine as a polycation for use in the invention. Polylysine is a polymer comprising attached positively charged branching groups which are also present in HIV-TAT because lysine is present in HIV TAT. Use of polylysine in the formation of complexes with plasmid DNAs comprising selectable markers would render these claims obvious.

Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the elements of the invention of Illum into a kit because one

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of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

Claims 19, 24, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Puls et al (Gene Therapy 6: 1774-1778, 1999) in view of Luo et al (US Patent 6,280,937) and

http://www.genlantis.com/catalog/product_line.cfm?product_family_key=13&product_line_key=54, retrieved from the internet on 9/2/05.

Puls taught non-covalent complexes of polylysine and plasmid pGeneGrip encoding green fluorescent protein (GFP) under the control of a CMV promoter and a selectable marker (see map on second page of attached product information downloaded from the web site cited above). The polylysine comprised an attached antibody targeting ligand which is considered to be an efficiency group. See abstract. Regarding claims 11, 12 and 21, polylysine is a polymer comprising attached positively charged branching groups, i.e. domains, which are also present in HIV-TAT because lysine is present in HIV TAT.

Puls did not teach a nucleic acid encoding blue fluorescent protein.

Luo taught that blue fluorescent protein and green fluorescent proteins could be used as alternative markers for detection. See column 6, lines 45-57. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-

recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (J. Biol. Chem. 262(10): 4429-4432, 1987) in view of GenBank Accession No. M77788 (2005).

Wu taught non-covalent complexes of plasmid pSV2 CAT and polylysine, wherein the polylysine comprised an attached asialoorosomucoid targeting ligand. See abstract. Plasmid pSV2 CAT comprises a selectable marker (beta lactamase, i.e. ampicillin resistance) as evidenced by GenBank Accession No. M77788. The selectable marker is considered to be a persistence factor as required by claim 39.

Wu did not teach organization of the polycation and nucleic acid into a kit.

It would have been obvious to one of ordinary skill in the art at the time of the invention to organize the elements of the invention of Wu into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 9/7/06 have been fully considered but they are not persuasive.

Applicant addresses the rejection of Illum at pages 20 and 21 of the response. Applicant reiterates arguments that double stranded DNA does not comprise two negatively charged "members" as claimed, because one of ordinary skill in the art would consider the term DNA to refer to double stranded, hybridized DNA, and not to single stranded DNA. This is unpersuasive for the reasons set forth above and because double stranded DNA, by definition, has two strands, each of which is a negatively charged backbone.

Applicant argues that the side chains found in polylysine are structurally distinct from those discussed at page 9 of the specification. This is unpersuasive. The claims recite that the positively charged branching groups or efficiency groups can be any HIV-TAT fragment. As discussed above, HIV-TAT comprises a trilycine group, so any lysine pair or triplet in polylysine is a fragment of HIV-TAT, and meets the structural requirement of claim 19 and dependents. Also with regard to claim 1 and dependents, the side chain of lysine can be considered to be a positively charged branching group that is a fragment of HIV-TAT, because HIV-TAT contains lysines.

Applicant addresses the rejection over Puls in view of Luo at page 22 of the response. Applicant's arguments are based on the position that Puls does not teach an

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efficiency group as recited in amended claim 19, and Luo does not alleviate this deficiency. This is unpersuasive for the reasons set forth above under 102 rejections, i.e. Puls anticipates claim 19. Applicant has not presented any reason why the references are not combinable, so the rejection is maintained.

Finally, Applicant argues that Wu fails to render claim 39 obvious for the same reasons set forth in the discussion of the 102(b) rejection over Wu. These arguments are unpersuasive for the reasons set forth above.

Conclusion

No claim is allowed.

This is a request for continued examination of applicant's earlier Application No. 09/910,432. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

A handwritten signature in black ink, appearing to read 'RSC', with a long horizontal line extending to the right.

Richard Schnizer, Ph.D.
Primary Examiner
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